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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,773	01/16/2004	Seng H. Cheng	07680.0018	6298

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,773	CHENG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-12,14-18,20,22,36-38 and 40-47* is/are pending in the application.

4a) Of the above claim(s) *10-12,22 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6-9, 14-18, 20, 36-38 and 40-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-3-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 12-3-07 has been entered. Claims 1, 3, 6, 8, 14-18, 20, 36-38 and 40 have been amended. Claims 13, 19 and 39 have been canceled. Claims 41-47 have been added.

1. Newly submitted claim 47 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 47 depends from claim 10, which is drawn to non-elected subject matter.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 47 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 3, 4, 6-12, 14-18, 20, 22, 36-38 and 40-47 are pending. Claims 1, 3, 4, 6-9, 14-18, 20, 36-38 and 40-46 are considered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3, 4, 6-9, 14-18, 20, 36-38 and 40 remain rejected and newly added claims 41-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention. Applicant's arguments filed 12-3-07 have been fully considered but they are not persuasive.

Claim 1 has been amended to limit the gene therapyvector to AAV vector and the tissue specific regulatory element is a liver-specific regulatory element. Claim 20 has been amended to limit the gene therapy vecto to AAV vector. The newly added claims 41-46 specify the liver-specific regulatory element is DC190, the lysosomal storage disease is Niemann-Pick disease or Gaucher disease and the lysosomal hydrolase is sphingomylinase.

Applicants cite references Ziegler, Barbon, McEachern and FDA approved treatments Fabrazyme and Replagal, and argue that the specification provide adequate guidance for the claimed invention and the references provide evidence that four distinct lysosomal storage diseases can be treated using the claimed methods (amendment, p. 10-12). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07. Ziegler teaches preparation of Ad2/CEHalpha-Gal and Ad2/CMVHIalpha-Gal recombinant adenoviral vectors and said viral vectors were injected through tail vein of Fabry (-/-) mice, and shows elevation of alpha-galactosidase A activity in liver, lung and kidney etc, and significant reduction in GL-3 content in the tissues for up to 6 months posttreatment (e.g. abstract, materials and methods). As discussed in the preceding Official action mailed 6-1-07, the claims encompass treatment of any lysosomal storage disease in a subject by first administering any AAV vector encoding a lysosomal hydrolase under the control of a liver-specific regulatory element and then administering an exogenously produced natural or recombinant lysosomal hydrolase to a subject via various administration routes or treatment of a subject having Fabry disease comprising first administering any AAV vector encoding alpha-galactosidase A under

the control of a human albumin promoter and 2 copies of a human prothrombin enhancer and then administering an exogenously produced natural or recombinant alpha-galactosidase A via various administration routes. The claims read on using polynucleotides encoding various lysosomal hydrolases to treat various lysosomal storage diseases in a subject and this includes treating a lysosomal storage disease with a non-corresponding lysosomal hydrolase. There are numerous different lysosomal storage diseases that caused by the deficiency of numerous different lysosomal hydrolase and even the cause of some lysosomal diseases are still unknown, such as CLN 4, CLN 6 and CLN7 (see Table I of Wraith et al., 2001, cited by applicant in the amendment filed 12-3-07). The specification fails to provide adequate guidance and evidence for how to treat different lysosomal storage disease with a non-corresponding lysosomal hydrolase and how to treat a lysosomal storage disease with unknown cause. The claims read on gene therapy in vivo and the art of gene therapy in vivo was unpredictable at the time of the invention. Administration route of an expression construct expressing a gene product of interest plays an important role in gene transfer *in vivo*. The fate of DNA construct, the amount of DNA reaches its targeted site, the stability of mRNA and protein expressed, and the biological function of the protein all depend on the administration route in gene transfer *in vivo*.

Further, the state of the art of treating lysosomal storage diseases in vivo was unpredictable at the time of the invention as evidenced by the reports of Pastores, Wraith and Eto. Lysosomal disorders (LSDs) are inborn errors of metabolism associated with a disruption in the hydrolysis and transport of diverse macromolecules within the endo-lysosomal compartment. About 50 distinct clinical entities are classified within this disease group and characteristics features of an LSD may include dysmorphic facial features, organomegaly, skeletal problems

and CNS dysfunction. There is broad heterogeneity in clinical expression within disease types, which, in the single hydrolase-deficiency disorders, partly reflects the presence or absence of residual enzyme activity and the wide variability in clinical expression for most subtypes, even among affected members of the same family, suggests that ultimate disease course is likely to be influenced by several modifiers. Diseases associated with primary CNS involvement present major challenges that are beyond the access limitations imposed by the blood- and CSF-barrier. Beyond the issues relating to treatment of the CNS pathology, the multisystemic nature of LSDs and the possibility of "sanctuaries" (i.e., tissue sites of storage that may not be fully accessible to small molecules, enzyme- or cell-based therapy; or may be unresponsive to therapy because of alternative downstream disease mechanisms that may be irreversible) raise the prospect that only partial responses may occur, despite prolonged treatment. There is an inability to target the infused enzymes to specific sites of pathology, especially the central nervous system and a lack of suitable animal models of the human disease in which to evaluate the new therapy (intravenous infusion of lysosomal enzymes). In view of the diverse lysosomal storage diseases or disorders, the broad scope of heterogeneity of clinical expression within a type of LSD, limited number of enzyme replacement therapy available, and the difficulties in treating LSDs involving CNS, one skilled in the art at the time of the invention would not know how to treat various LSDs by using any AAV vector expressing various lysosomal hydrolases under the control of a liver specific promoter in combination with an enzyme replacement therapy via various administration routes such that therapeutic effect can be obtained and pathological symptoms can be ameliorated in vivo.

Ziegler only teaches reduction of GL-3 content, however, the GL-3 accumulation is only a metabolite accumulation due to the lack of alpha-Gal but not the pathological symptoms of the Fabry disease. As discussed above, there are diverse pathological symptoms of different LSDs and broad scope of heterogeneity of clinical expression within a type of LSD. There is no correlation between reduction of GL-3 level in the organs and treatment of Fabry disease in a subject, i.e. amelioration of pathological symptoms of Fabry disease in vivo. Reduction of GL-3 in organs in a subject might mean correction of the metabolite concentration but it does not necessarily mean that the Fabry disease is treated. It is noted that the Ad2/CEHalpha-Gal disclosed by Ziegler is not the same as Ad2/CMVHIalpha-Gal, which contains both CMV enhancer and promoter sequences (see Ziegler, p. 1668, right column, 1st full paragraph). Evidently, the Ad2/CEHalpha-Gal vector is not the same as the AAV2/DC190-alphagal as disclosed in the instant invention. Different promoter or enhancer used would have different effect on the expression level of the desired gene product in vivo.

Barbon teaches that there are two type of Niemann-like disease. "Type A Niemann-Pick disease is a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and a rapidly progressive neuro-degenerative course. In contrast, patients with type B disease are usually nonneuropathic, exhibiting primarily liver, spleen, and pulmonary involvement, with survival possible into adulthood" (e.g. p. 431, left column). Barbon teaches that AAV8/DC190-hASM vector ($3x10^{10}$ particles) generated a level of expression about 10 fold higher than that from $3x10^{11}$ particles of the AAV1/DC190-hASM vector (e.g. p. 438, left column, 1st paragraph). This shows different AAV vectors could result in different expression level of the human acid sphingomyelinase (hASM) and different therapeutic effect in vivo. The AAV

vectors disclosed by Barbon are different from the vectors of the instant invention and the specification of the instant invention fails to disclose the vectors of Barbon. Therefore, the disclosure of the post-filing Barbon reference fails to enable the instant invention. Further, AAV8 vector was injected via tail vein but not any other administration routes. The specification fails to provide adequate guidance for how to correct the metabolic defect in the visceral organs of a mouse model of Niemann-Pick disease via other administration route, such as oral administration and topical administration. Even if the AAV-8 vector can be used to treat type B Neimann-Pick disease, it is not enabled to treat type A Niemann-Pick disease because of the pathology of type A Niemann-Pick disease discussed above.

Similarly, McEachern teaches using AAV8 vector expressing glucocerebrosidase under the control of a DC172, which is different from the AAV vectors disclosed in the instant invention. The disclosure of the post-filing McEachern reference fails to enable the instant invention. As discussed above, there are diverse pathological symptoms of different LSDs and broad scope of heterogeneity of clinical expression within a type of LSD. There is no correlation between reduction of GL-1 level in the organs and treatment of Gaucher disease in a subject, i.e. amelioration of pathological symptoms of Gaucher disease in vivo. Reduction of GL-1 in organs in a subject does not necessarily mean that the Gaucher disease is treated.

Examiner is unable to locate the evidence of FDA-approved treatment of Pompe disease in the amendment filed 12-3-07, therefore, such argument renders moot. Further, an FDA-approved treatment of Pompe disease does not mean that Pompe disease can be treated and the instant invention is enabled. The claimed invention encompasses treating numerous different LSDs with different lysosomal hydrolases via various administration routes. The state of the art

of gene therapy and protein therapy are unpredictable at the time of the invention and they have to be considered individually. The therapeutic effect in vivo depends on the vector, the promoter, the coding sequence, the non-coding sequence, administration route used, the subject to be treated and the type of disease treated. One skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that although LSDs may be diverse, they share an underlying mechanistic similarity, complete or partial lack of enzymatic activity of a particular lysosomal hydrolase and such heterogeneous clinical manifestations do not necessitates heterogeneous treatments (amendment, p. 12-13). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above. LSDs may be due to complete or partial lack of enzymatic activity of a particular lysosomal hydrolase, however, different lysosomal hydrolases have different enzymatic activities that would result in diverse pathological consequences of varying degrees in different organs and/or cell types in a subject, i.e. it may not be limited to liver. The treatment of LSDs has to be considered individually. As discussed above, the cause (the type of enzyme deficiency) of some LSDs are still unknown. The specification fails to provide adequate guidance and evidence for how to ameliorate pathological symptoms of various LSDs in vivo by using AAV vector expressing various lysosomal hydrolases or non-corresponding hydrolase under the control of various promoters or liver-specific promoter/enhancer. Absent such guidance and evidence, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the sequences encoding different lysosomal enzymes were known in the art and a skilled artisan would know how to identify the sequences or variant sequences for use in enzyme replacement therapy or gene therapy (amendment, p. 13-14). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above. The biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and one skilled artisan would require undue experimentation to identify the biological function of various lysosomal hydrolases and their variants, and their therapeutic effect in treating various LSDs in vivo.

Applicants Cite FDA-approved treatment of Fabry disease and argue that accumulation of GL-3 is a measure of disease progression and the cited Wraith reference (2006) that the natural history of the disease should be altered favourably when the level of storage within the cells or organs is reduced (amendment, p. 14-15). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above. Again, Examiner is unable to locate the evidence of FDA-approved treatment of Fabby disease in the amendment filed 12-3-07. Reduction of accumulated metabolite in LSDs may be a good beginning of treating LSDs, but it does not mean that the diverse pathologic symptoms of various LSDs would be ameliorated because of the reasons set forth above.

Applicants argue that the instant invention is directed to a method that overcome significant limitations associated with gene therapy ...when used alone. Applicants cite Salvetti and argue that LSDs present a favourable situation for gene therapy, low and unregulated levels of enzyme activity should be sufficient for correction (amendment, p. 15-16). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the

reasons set forth above. Salvetti only speculates that LSDs may be good model for gene therapy, however, there is no evidence to support that the full scope of the invention claimed in the instant invention is enabled.

Applicants cite various literatures regarding gene therapy for lysosomal storage diseases and argue that the claimed invention is enabled (amendment, p. 16). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above. The cited reference Wraith (2001) in the amendment filed 12-3-07 reports that "the early onset, progressive nature, and tendency to involve the CNS have always been regarded as major hurdles to effective treatment" and "a feature of majority of LSDs is the great clinical variability in diseases associated with a single enzyme defect" (e.g. p. 639, left column). Wraith points out that in 300 human trials of LSDs gene therapy, it is debatable whether any has shown any persistent therapeutic benefit (e.g. p. 644, left column, 2nd paragraph).

Applicants argue that the claims have been amended to read on using liver-specific regulatory element (amendment, p. 17). This is not found persuasive because different LSDs could have pathological consequences in organs and cells other than liver. It is unclear how the liver-specific regulatory sequence would be able to provide sufficient expression of desired lysosomal hydrolase in cells and organs other than liver so as to provide therapeutic effect in said cells and organs for treating LSDs.

Applicants cite various references and argue that ERT was approved for treatment of Gaucher disease and a number of ERT therapies have been approved and commercially marketed (amendment, p. 17-18). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above.

Applicants argue that it is improper to request evidence regarding the degree of effectiveness and treatment of non-CNS aspects of a LSD may be helpful to patients exhibiting neurological symptoms (amendment, p. 19). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above. Applicants must provide sufficient enabling disclosure for the full scope of the claimed invention but fails to do so in view of the unpredictable nature of the art and the vast scope of the invention claimed. The statement "treatment of non-CNS aspects of a LSD **may be** helpful to patients exhibiting neurological symptoms" does not mean that the claimed invention is enabled. "Improved quality of life" does not mean that the LSD is treated and the pathological symptoms are ameliorated.

Applicants argue that mere presence of inoperative embodiments is not grounds for an enablement rejection and most enzymes implicated in LSD are secreted proteins (amendment, p. 20). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above. Applicants must provide sufficient enabling disclosure for the full scope of the claimed invention but fails to do so in view of the unpredictable nature of the art and the vast scope of the invention claimed.

Applicants argue that a patent need not teach what is well known in the art and the specification teaches methods for administering the combination therapies of the invention include all methods well known in the art (amendment, p. 21). This is not found persuasive because of the reasons set froth in the preceding Official action mailed 6-1-07 and the reasons set forth above. Although method of administration was known in the art, however, applicants must

provide sufficient enabling disclosure for the full scope of the claimed invention but fails to do so in view of the unpredictable nature of the art and the vast scope of the invention claimed.

Conclusion

No claim is allowed.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.